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EDITORIAL

A POTENTIAL DANGER

THE Medical Research Council's report on "The Hazards to Man of of Nuclear and Allied Radiations" (1956, H.M.S.O.) draws attention to the dangers inherent upon the use of nuclear weapons, X-ray machines and various other sources of harmful radiation such as cosmic rays, isotopes and even television sets and luminous watches.

It is hoped that veterinary surgeons will never be called upon to face the dangers associated with the use of nuclear weapons; it may be that radio isotopes will be used for therapeutic and diagnostic purposes in the near future, but whilst one should be prepared to meet and combat harmful radiations from these sources, the hazard is not an immediate one and shows only as a small cloud the size of a man's hand in a fair sky.

X-ray machines are with us, they are in frequent and sometimes constant use in many practices and it is well to remember that these machines, even those of most modern construction, are not entirely free from the dangers which wrought their ill-effects upon the pioneer workers. Since 1895 when Röntgen discovered the short-wave length electro-magnetic radiations called X-rays, many operators have been maimed and mutilated whilst others have suffered from ill-health the signs and symptoms of which are not so manifest yet the long-term effects can be equally tragic.

(The June issue of The British Veterinary Journal was published on June 27)

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The obvious injuries suffered by the pioneers could not escape notice and their sacrifice stimulated the physicists to search for the means of protection. Many of the methods devised have been incorporated in the structure of modern instruments and protective clothing has been designed for the operators. There is no doubt that many of the grave and lethal factors associated with the act of radiography have been brought under control and danger has been reduced to a minimum. Unfortunately, these precautions have led to a feeling of security and especially so to those who are not entirely conversant with the properties of X-rays and whose senses are dulled by the absence of obvious immediate effects.

No matter how well the machine or the operator is screened, mishap can occur. The operator may be outside the direct line of the rays but such is their strength that they may be reflected and "scatter" over a relatively wide area. The dose emanating from "scatter" may be small but one must remember that the effect is cumulative and small doses constantly administered over a long period can be as potent as the same dose received on one or two occasions.

X-rays are such a valuable adjunct to the art of clinical diagnosis and the modern "press-button" machine can be operated by a novice that in many veterinary surgeon's premises the X-ray machine is one of the most obvious and frequently used instruments. Owing to the ease with which they can be used for the detection of foreign bodies, etc., the fluorescent screen is often in constant use. The danger in using a fluoroscope is much greater than the production of films. The operator may be so intent on the view that he may neglect to confine the beam within the limits of the screen. A physicist entering upon such a scene would shudder with horror.

This editorial is written not with any idea of condemning the use of X-rays in veterinary practice but rather with the view in mind that "Here is a most valuable aid to clinical diagnosis when used with due care." If that care be not exercised then it can become a grave and serious source of danger. Means have been devised to combat this danger. Use them on all occasions.

We have not attempted to discuss the physical properties of X-rays or their applications, for in a subsequent issue we hope to publish an article dealing with these matters by competent authorities. The purpose of this editorial comment is to draw attention to a serious danger which may be avoided if care is exercised.

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GENERAL ARTICLES

FURTHER EXAMPLES OF SPONTANEOUS NEOPLASMS IN THE DOMESTIC CAT

By E. COTCHIN

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A REPORT was published in 1952 of 226 neoplasms of domestic cats examined in the Department of Pathology of the Royal Veterinary College in the period January, 1940, to March, 1952 (Cotchin, 1952). Since then, a further 200 neoplasms from cats have been examined macroscopically and histologically. In this later series, 64 neoplasms were from cats on which post-mortem examinations were made personally, while 59 were specimens (referred to later as post-mortem specimens) which were removed from cats by veterinary surgeons who noted obvious metastases. Thus, for 123 of the total of 200 neoplasms, there is information as to the presence or absence of metastases.

System of Origin.

The system of origin of the 200 tumours is shown in Table I.

Table 1.

Systems of origin of 200 spontaneous neoplasms in cats.

System	Number of tumours	Percentage
Alimentary	56	28
Cutaneous	32	16
Genital	25	12.5
Lymphatic	25	12.5
Skeletal	16	8
Urinary	14	7
Ear	8	4
Respiratory	4	2
Eye	2	1
Endocrine	2	1
Miscellaneous and unknown	16	8
	200	100

Sex Incidence.

The sex of the affected cat was known in 150 instances: 101 were males, of which 91 were castrated, and 49 were females, of which 19 were castrated. One of the entire males was a bilateral abdominal cryptorchid. Information about the sex of the affected animals in respect of the tumours of the different systems is shown in Table II.

Age Incidence.

The ages of 160 affected cats were known, and ranged from under 1 to more than 20 years. The average age was $9\frac{1}{2}$ years.

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Age (years)	less than 1	1	2	3	4	5	6	7	8	9	10
No. of cats	1	0	4	5	10	6	10	10	20	16	19

11	12	13	14	15	16	17	18	19	20	Over 20
11	10	10	11	9	4	2	0	0	1	1

Table II

Sex of cats bearing tumours in different systems

System of origin	Sex				Number of cats of which sex was known
	Male		Female		
	Entire	Castrated	Entire	Castrated	
Alimentary	3	37	3	2	45
Cutaneous	3	15	1	3	22
Genital	0	1	19	5	25
Lymphatic	2	11	2	1	16
Skeletal	0	8	1	3	12
Urinary	0	5	2	2	9
Ear	1	2	0	1	4
Respiratory	1	0	1	0	2
Eye	0	1	0	0	1
Endocrine	0	1+	0	0	1+
Others	0	10	1	2	13
	10	91	30	19	150

+The second tumour in this system was in a castrated male, included under "alimentary", as it had neoplasms in both systems.

Description of the Tumours of the Different Systems

(1) Alimentary System

The types of tumour, and other relevant data, are recorded in Table III.

Table III

Sites of origin, and neoplastic types, of 56 primary neoplasms of the alimentary system of cats, with age and sex incidence, and occurrence of metastases.

Site of origin and number of tumours		Types of tumour and number		Age (years)	Sex				No. with metastases
					m.	c.m.	f.	c.f.	
Tongue	9	Squamous-cell carcinoma	9	7-14	1	3	1	-	1
Tonsil	5	Squamous-cell carcinoma	5	10-15	-	1	-	1	3
Gum	11	Squamous-cell carcinoma	9	9-16	-	7	-	1	3
		Sarcoma	1	17	-	1	-	-	
		Epulis	1	10	-	1	-	-	
Oesophagus	5	Squamous-cell carcinoma	5	6-16	-	5	-	-	1
Stomach	1	Lympho-sarcoma	1	9	-	1	-	-	1
Intestine	19	sarcoma	15	4½-15	1	10	1	-	10
		carcinoma	4	5-9	1	3	-	-	3
Liver	1	Bile-duct carcinoma	1	9	-	1	-	-	1
Pancreas	5	carcinoma	5	6-15	-	4	1	-	4
	56		56		3	37	3	2	27

m. = male; c.m. = castrated male; f. = female; c.f. = castrated female

(*a*) *Tongue.*

The nine tumours were all squamous-cell carcinomas, of which seven showed keratinisation, and all had a marked fibrous stroma. The ages of five of the affected animals ranged from 7 to 14 years. (In this group (as in others), the average (of 10 years) is misleading, as the affected cats were 7, 7 and 8 years old on the one hand, and 13 and 14 years on the other.) There were four males (three castrated) and one entire female. The symptoms reported were of salivation and of difficulty in eating. The tumours all developed on the ventrolateral surface of the tongue as firm, whitish, nodular masses, which usually protruded to a moderate extent only, but in all cases showed extensive invasion of the muscle of the tongue. A post-mortem examination was made in three cases, and post-mortem specimens were examined from five. Metastasis (to the right mandibular node) was found in one cat only.

(*b*) *Tonsil.*

The five tumours were all keratinising squamous-cell carcinomas. The affected animals ranged from 10 to 15 years of age (four cats). The sex of two cats was recorded—one castrated male, one castrated female. The symptoms were of difficulty in swallowing. The tumours affected the left tonsil three times and the right twice. They were nodular firm masses, quite small, whitish in colour. Three of the cats were examined post-mortem, and post-mortem specimens were received from the other two. Metastases were present in three cats—in each case in the superior cervical node.

(*c*) *Gum and Palate.*

Nine of the 11 tumours were squamous-cell carcinomas, of which all but one showed keratinisation. The ages of the affected animals ranged from 9 to 16 years. Seven of the cats were castrated males, and one was a castrated female. The tumours were from the gum of the upper jaw in three of the cats, the gum of the lower jaw in three, and the mucosa of the hard palate in two; the exact site, whether gum or palate, was not specified in one. The lesions occurred as ulcerating infected swellings. The palatine tumours bulged upwards into the nasal passages, and the gum tumours invaded deeply into the underlying bone, which was considerably swollen.

Post-mortem examination was made of six animals and post-mortem specimens from two others were examined. Metastases were detected in three cases—in two instances in the regional superior cervical lymph node (and in one also in the prescapular node) and in the third in the lung, a bronchial node, and the myocardium of the left ventricle.

One of the other two tumours was a bony epulis of the mandible of a 10-year-old castrated male cat, and the other a giant-cell sarcoma of the gum of a 17-year-old castrated male cat.

(*d*) *Œsophagus.*

The five tumours were all squamous-cell carcinomas, of which three showed keratinisation. The five cats were from 6 to 16 years of age and all were castrated males. The symptoms were of increasing œsophageal obstruction,

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vomiting occurring more or less immediately after swallowing solid food. The lesions in three cats were almost-annular whitish growths just inside the entrance to the chest; the other two were in the cervical part of the œsophagus, one being rather diffusely extended over much of its length. Post-mortem examination was made of four animals, and post-mortem specimens were received from the fifth. Metastasis, to a mediastinal lymph node, was present in one cat with a tumour of the thoracic part of the œsophagus.

(*e*) *Stomach.*

A 9-year-old castrated male cat, which had been unwell for six months, with loss of appetite and wasting, was destroyed after exploratory laparotomy had shown a diffuse greyish-white thickening of much of the wall of the stomach. The tumour, a rather pleomorphic sarcoma composed of rounded cells, was found at post-mortem examination to have spread to a local node.

(*f*) *Intestines.*

Of the 19 tumours, 15 were sarcomas and four were carcinomas.

Six of the 15 sarcomas were lymphosarcomas and three were spindle-cell sarcomas (probably leiomyosarcomas); four were round-cell sarcomas, not sufficiently characteristic to be called lymphosarcomas, and two were pleomorphic, partly giant-cell, sarcomas. Thirteen of the cats were from $4\frac{1}{2}$ to 15 years of age. Ten were castrated males, one was an entire male, and one an entire female. The symptoms were chiefly of intestinal obstruction, with the development of a palpable abdominal mass, which sometimes proved to be the neoplasm itself, but was sometimes the metastatic lesions in mesenteric or ileocolic nodes, or in the kidneys. In one instance the colon alone was affected, in another, lesions were present in the duodenum and ileum, whilst the rest of the tumours involved the small intestine: these were chiefly in the region of the ileum, and in two cases involved the first part of the large intestine also. The lesions appeared as greyish-white regional thickenings of the bowel-wall, of variable and usually quite soft consistency, with a rather homogeneous appearance on the cut surface, and variable, sometimes extensive, local tissue hæmorrhage.

Post-mortem examination was made of six cats, and post-mortem specimens were received from seven others. Metastases were present in ten cats; they involved the mesenteric and/or ileocolic nodes in at least seven, the liver (eight), kidneys (five), spleen (four), lungs (three), myocardium, retina, and pituitary region (one each).

The four carcinomas were mucoid adenocarcinomas, with, in one tumour, bony metaplasia of the stroma. The ages of three of the affected cats were 5, 6 and 9 years. Three were castrated males, and one was an entire male. The symptoms were of increasing intestinal obstruction, loss of weight, and a palpable abdominal mass. The tumours occurred in the jejunum in three cats, and in the ileum in the fourth. They appeared as regional thickenings of the intestine by firm whitish tissue, in one case with small mucoid cysts. One cat was examined post-mortem, and three provided post-mortem specimens. Metastases were found in three—the mesenteric node, mesentery, or omentum being involved.

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(*g*) *Liver.*

A 9-year-old castrated male cat on post-mortem examination showed a mucoid bile-duct carcinoma, with local spread to the posterior surface of the diaphragm and wall of the stomach, and metastasis to the lungs.

(*h*) *Pancreas.*

The pancreatic origin of four of the five tumours was diagnosed on histological grounds only, as the exact origin of the tumour in the pancreas could not be identified definitely. The tumours were all adenocarcinomas of exocrine tissue. The ages of the five affected cats ranged from 6 to 15 years. Four were castrated males, the fifth an entire female. Symptoms included loss of condition, inappetance and occasional vomiting. The tumour tissue was greyish-white and firm. Two cats were examined post-mortem, and post-mortem specimens were received from two others. Metastases were present in four cats—in three in the liver, and in one in the omentum.

(2) Cutaneous System

The 32 tumours of the skin and subcutaneous tissue (excluding the ear) comprised 15 of epithelial origin, 13 of connective tissue origin, and four of uncertain type. The ages of 28 of the animals ranged from 3 to 16 years. Fifteen of the cats were castrated males, three were entire males, one was an entire female, and three were castrated females.

The 15 epithelial tumours comprised:—

(*i*) Eight basosquamous tumours, of which five appeared as epithelial cysts. These tumours, which occurred in the neck region in four animals, were oval, well-defined dermal structures, three of which showed a greyish or blackish mottled surface. Of the five cystic ones, three were filled with a slimy fluid, and two showed a solid plug of keratinised cells. The lining epithelium was of basosquamous type, much folded, and usually pigmented with melanin-containing cells.

(*ii*) Four squamous-cell carcinomas, producing varying amounts of keratin. In two there were scattered, notably large, single nuclei, accompanied in one specimen by multinucleated epithelial cells.

(*iii*) The three others comprised: (*a*) a solid carcinoma apparently of skin gland origin, of the left inguinal region, which had metastasised to the regional node; (*b*) one case of multiple basosquamous lesions, presumably carcinomas as local tissue invasion was present, although no metastases were found on post-mortem examination; (*c*) a sebaceous adenoma.

The 13 connective tissue tumours comprised:—

(*i*) A lipoma, near the mammary gland of an 8-year-old castrated female cat.

(*ii*) Twelve sarcomas of various histological types, classified as fibrosarcoma (four), leiomyosarcoma (two), sarcoma of round cells (two), pleomorphic cell sarcoma (two), myxosarcoma and angiosarcoma (one each). One of the sarcomas of round cells was a post-mortem specimen from the left mandibular skin of a 10-year-old castrated male cat.

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(3) Genital System

Apart from one cat (a 12-year-old female with multiple uterine fibro-leiomyomas), there were 24 cats with mammary tumours. The 24 mammary tumours comprised 21 adenocarcinomas, one squamous-cell carcinoma and two benign cystic adenomas.

The 21 adenocarcinomas occurred in cats whose age (20 animals) ranged from 5 years to 16 years. There were 17 entire females, three castrated females (at least one of which had been castrated late in life) and one castrated male. The gland of origin was recorded in 13 instances (anterior gland 10, abdominal 1, posterior 2). The tumours were generally flattened, ulcerated, firm, nodular grey-white structures, with variable local muscle invasion. Post-mortem examination was made of five of the cats, and post-mortem specimens were received from one other. There were metastases in seven of the 21 cats—affecting the regional lymph node (six cats), lungs (five), pleura (one), mediastinum (one) and kidney (one).

The one squamous-cell carcinoma arose in the region of the right penultimate mamma. There was a single cystic adenoma in a mamma of a 10-year-old castrated female, while all the glandular tissue of an adult entire female showed diffuse glandular enlargement, due to what appeared to be adenomatous proliferation.

(4) Lymphatic System

Of the 25 neoplasms in this system, 11 appeared to be primary in the mesenteric lymph node, five affected chiefly the spleen and three the anterior mediastinum, three were generalised as lymphatic leukosis, while three occurred in more or less isolated nodes and organs.

(*a*) *Mesenteric node.*

The 11 tumours comprised four lymphosarcomas, and seven tumours of more pleomorphic cell type, with a more or less marked tendency to spindle-cell formation. In three tumours, multinucleate giant cells were prominent. Three tumours appeared to be angiosarcomas. The ages of nine affected cats ranged from 2 to 15 years. Six of the cats were castrated males, one was an entire male, and one was a castrated female. The symptoms were loss of weight and the development of a palpable mass in the abdomen. The tumours were generally oval in shape, up to 6 cm. long, rather soft, grey-white on the cut surface, with variable and sometimes extensive hæmorrhagic areas. The ileocolic node was often involved in addition to the mesenteric node. Post-mortem examination was made in four instances, and post-mortem specimens were examined from six others. Neoplastic tissue similar to that in the mesenteric node tumour was found in six cats—in the liver (three), lung, spleen and thymus (one each).

(*b*) *Spleen.*

The five tumours appeared to be diffuse reticulum-cell sarcomas. The affected animals were 3, 3, 9, 9 and 11 years old respectively. Two were castrated males, and two entire females. The symptoms were of loss of appetite and abdominal distension, with a palpably-enlarged spleen. The organ was

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diffusely swollen, up to 20 cm. in length and 355 g. in weight, and showed a reddish-grey cut surface. Post-mortem examination was made of one cat, and similar neoplastic cells were found in the liver and myocardium. A second spleen was a post-mortem specimen. The other three were all removed at operation.

(*c*) *Anterior mediastinum.*

Lymphosarcomas developed in the anterior mediastinum of three cats, causing dyspnœa. One animal, an 8-month-old castrated male, was severely dyspnœic: the post-mortem specimen of a grey-white, rather friable mass in the anterior mediastinum is thought to have developed in the thymus. A second tumour was a post-mortem specimen of a similar lesion in the anterior mediastinum of a cat of unspecified age. The third cat, a 17-year-old entire male, showed a lymphosarcoma of the anterior mediastinum, which had invaded the right lung.

(*d*) *Lymphatic leukosis.*

Three cats with lymphatic leukosis were examined post-mortem. The first, a 5-year-old castrated male, showed general enlargement of the body nodes, and a heavy involvement of the liver. The second, an 8-year-old cat, showed, besides the general enlargement of body nodes, which was particularly marked in the neck, a mass in the lower neck and anterior mediastinum, 12 cm. long, up to $3\frac{1}{2}$ cm. wide, and up to 4 cm. deep. The fatty bone marrow was involved, but not the liver. The third, an 8-year-old castrated male, showed a generalised enlargement of the superficial nodes, chiefly in the superficial inguinal, precrural, prescapular and axillary regions.

(5) Skeletal System

All the 16 primary tumours of this system developed in bones. Nine were osteogenic sarcomas, of which six produced a variable amount of bony matrix; six were chondrosarcomas, and one was a sarcoma of giant- and spindle-cells. The ages of 14 of the affected cats ranged from 2 to 20 years. There were eight castrated males, one entire female, and three castrated females. The bones of origin were: humerus (five), femur (three), superior maxilla (two), mandible, scapula, radius, lumbar vertebra and ilium (one each). The tumours appeared as firm, fibrous, variably calcified whitish masses, frequently very large when affecting a limb bone. There was usually considerable destruction of the affected bone. Post-mortem examination was made of 11 animals and post-mortem specimens were obtained from the others. Metastases were found in three cats, with neoplasms of radius (spleen secondary), femur (lung secondary) and humerus (secondaries in regional node and lung).

(6) Urinary System

There were 13 instances in which the kidney was involved, and one in which the urinary bladder showed a neoplasm: the latter was a post-mortem specimen from a 13-year-old castrated male cat—one half of the bladder wall was diffusely thickened, and showed, histologically, carcinoma cells in small, scattered group lying amongst bundles of hypertrophied smooth muscle.

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The 13 kidney neoplasms included an embryonal nephroma of the right kidney, a post-mortem specimen from a 2-year-old castrated male cat. The kidney measured 10 x 9 cm., and showed a grey, rather soft tissue, with central necrosis and hæmorrhage, and a thin rim of normal kidney tissue at one side. The tumour was of adenosarcoma type.

The other 12 tumours are included in the group of urinary system neoplasms because the main lesions, detectable clinically, were found in the kidney, but the fact that the lesions were commonly multiple, and that both kidneys were affected in at least nine cats, suggests that the lesions were not necessarily primary renal neoplasms. All were sarcomas: eight were lymphosarcomas, and the other four showed a more variable type of cell morphology, one approaching a leiomyosarcoma in appearance.

The ages of nine of the affected cats ranged from 3 to 22 years. There were four castrated males, two entire males, and two castrated females. The symptoms included thirst, inappetance, loss of weight, and the development of palpably enlarged kidneys. The lesions were of the type often called "sarcoma kidney." The cortex showed focal or diffuse widenings, often wedge-shaped, by whitish, rather soft tissue, contrasting in colour with the normal yellow cortex. The kidneys might reach 9 cm. in length and 5 cm. in width. Post-mortem examination was made of two cats, and post-mortem specimens were received from three others. Two of the affected kidneys had been removed at operation, and the opposite kidneys were not available for examination. Similar neoplastic tissue was present elsewhere in five cats—once in the uterus, once in the mesenteric node (histologically only), once in the myocardium, once in the thymus region. In one cat, similar neoplastic tissue was present in a mandibular node and in the brain by the pituitary.

(7) Ear

Of the eight tumours. five were keratinising squamous-cell carcinomas, and three were ceruminous adenocarcinomas. The squamous-cell carcinomas caused considerable deformity and destruction of the ear flap; at least three of them appeared to arise chiefly in the integument of the outer side of the ear, although the inner lining of the flap and of the external auditory canal was involved also. One of the cats was an entire male, one a castrated female. Post-mortem examination was made of two of the cats, and post-mortem specimens were examined from a third. No metastases were found, but there was extensive local invasion of the parotid lymph and salivary glands.

The three ceruminous adenocarcinomas occurred in cats which included animals three and four years of age, and two castrated males. None of the animals provided post-mortem material, so that the malignancy of the lesions was not confirmed.

(8) Respiratory System

The four tumours of this system comprised: a serous columnar-cell carcinoma of the nasal cavity of an aged female; a fibroma of the nasal cavity; a possible primary bronchial adenocarcinoma (a post-mortem specimen only was avail-

able); and a primary bronchial adenocarcinoma of an adult male cat (a bilateral abdominal cryptorchid) affecting a main bronchus in the main left lobe, with metastases in the liver and spleen.

(9) Eye

The two tumours were a tumour in the ciliary body (an anaplastic carcinoma) of the eye of a seven-year-old castrated male cat, and a melanoma of the corneoscleral junction of a 13-year-old cat. Both these lesions were removed at operation and the exact origin of the first tumour is undetermined.

(10) Endocrine System

The two tumours were a solid adenocarcinoma of the right thyroid gland of a 13-year-old castrated male cat, and a probable parathyroid adenoma of a 15-year-old castrated male cat, which had also a squamous-cell carcinoma of the œsophagus. The former tumour formed a well-defined brown friable mass in the position of the right thyroid gland. The latter, in the position of a left parathyroid gland, consisted of cells resembling clear cells of the parathyroid gland, arranged in sheets or trabeculæ. No endocrine effects were noted in either cat.

(11) Miscellaneous and Uncertain Tumours

In 16 instances insufficient material was received to provide a definite diagnosis of the type of tumour or of its origin.

Discussion

Over two-thirds of the 200 tumours in this series were found in one or other of four systems: alimentary (28 per cent), cutaneous (16 per cent), genital and lymphatic (each 12.5 per cent). None of the tumours appeared to originate in the central nervous system, nor in the male genital system (although one castrated male cat bore a tumour of the mammary gland).

The sex incidence is difficult to evaluate, as there is no information of the sex distribution of the total cat population, nor of the proportion of animals that are castrated. Of 600 of the total number of cats attending the Beaumont Hospital, for reasons other than castration or neoplasia, in the period roughly corresponding to the time of collection of the present series of tumours, 475 were males, of which 290 were castrated, and 125 were females, of which 52 were castrated. In the tumour-bearing series, there was a greater proportion of castrated males, but the significance of this is not known: it might merely reflect the well-known fact that many adult male cats are castrates. However, it appears that castration does not decrease the chances of developing a neoplasm.

Similarly, there is no information on the age distribution of the general population of cats. The 600 "clinic" cats referred to showed an average age of $3\frac{1}{2}$ years.

The important malignant tumours of the cat found in this series are: (1) Squamous-cell carcinomas of the upper part of the alimentary tract (tongue, gum and palate, tonsil, œsophagus)—over half of the tumours of the alimentary system occurred in the mouth or the œsophagus, and all but two of these were

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squamous-cell carcinomas: of these squamous-cell carcinomas, all but two occurred in castrated male cats; (2) sarcomas of the intestine and of the skin; (3) adenocarcinomas of the mammary gland; (4) lymphosarcomas; (5) sarcomas of the kidney.

Especial interest may be attached to the high incidence of carcinoma of the upper alimentary tract, which might possibly be due to the ingestion of some carcinogen; also, to the high proportion of malignancies in the series of mammary tumours; and thirdly, to the important incidence of lymphosarcomas. These findings are in general accord with those reported for the previous series of 226 cat tumours. A more extensive consideration of neoplasms in cats, based on these two series of tumours, will be given in a paper which is being prepared.

Summary

An account is given of the age, sex and site incidence of a series of 200 neoplasms from cats. The tumours of the different systems are briefly considered.

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JOHNE'S DISEASE

The theory behind herd complement-fixation testing and its proper usage in the field experiment in progress

By N. H. HOLE

Weybridge

COMPLEMENT-FIXATION methods for Johne's disease diagnosis have been studied at Weybridge for several years, and the Weybridge technique has recently been applied at several centres on the Continent and in New Zealand. It is generally agreed that it is a very useful and a reasonably accurate confirmatory test for suspected clinical disease, and it is used by practitioners quite widely in Great Britain for this purpose. This application of the test is undoubtedly of value in so far as it fills a gap in the laboratory approach to diagnosis, but this in itself does nothing toward the control or eradication of Johne's disease; once an animal has reached the stage of infection that makes it clinically suspect it has almost invariably scoured for a few days and left behind a mass of highly infective material to perpetuate the infection in other animals in the herd.

Various papers and reports have in the last few years made the economic importance of Johne's disease in cattle abundantly clear to all; many practitioners to-day consider it is a more serious problem for cattle than tuberculosis was at the commencement of attestation. Attempts at control or eradication have hitherto been desultory; the usual policy appears to have been one of hope that

the disease would die out or that some catholicon would turn up to-morrow While further intensive research into diagnostic and control methods is essential experiments with this disease are so protracted and uncertain that, instead of waiting for the discovery of perfect tests, an effort must be made *now* to utilise present knowledge to check the spread, even if methods have to be amended at a later date. Calf vaccination in Johne's disease is of proved value, but it interferes with the interpretation of the tuberculin test. With attestation approaching its goal after so many years of determined effort, it is obvious that so long as it is considered that the allergic sensitivity produced by vaccination is not clearly distinguishable from that caused by tuberculosis, such a means of controlling Johne's disease can have universal application only when other methods of control have failed. The only possible alternative at present available appears to be the use of a blood-testing method, and at Weybridge investigations are in progress to determine the practical value of the complement-fixation test for the elimination of the disease from infected herds. The inauguration of a considerable field experiment has, however, resulted in some misunderstanding of the claims made for herd testing, and the primary object of this note is to make quite clear the experimental nature of the work and to explain the theory and the evidence on which the trial has been based. An experiment is essentially a procedure the result of which is not known, executed in the hope that it will prove to be of value.

M. johnei is an obligatory parasite, and therefore in theory if infected animals can be prevented from distributing infection to others it should be possible to eradicate the disease. This is the basic principle in herd testing; it is hoped that the repeated application of the complement-fixation test and the eradication of the positives will remove all infected animals from the herd before they start to distribute infection. It is known that the test has its limitations, and that it must not be considered as anything like perfect. It appears to identify with consistency only animals with well-established lesions, possibly bowel lesions, but a reaction can nearly always be obtained before the onset of clinical symptoms. It is therefore quite unwarranted to expect one or two herd tests to clear out all the infected animals, because there are almost certain to be incubative or early cases that will only develop a blood reaction at a later stage. It has long been recognised that an infected calf may not develop a blood reaction for at least nine months, and how long a natural infection may remain dormant is not known. In spite of these limitations the herd-testing experiments are being continued because it is believed that not only does a blood reaction obtain in nearly every case before an animal scours but also that until scouring occurs the amount of infection distributed is negligible or nil.

It will be seen that the object of herd testing is to enable young stock to be reared free from infection; that no assumption of success will be permissible until calves born after herd testing commenced have themselves had two or three calves without showing evidence of Johne's disease; that the prospects of success depend on the veracity of the opinion that no appreciable amount of infection is spread before an animal scours, and that a very high proportion of

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infected animals react to the blood test before they start to scour. Failure can be recognised only when animals born after the experiment commenced, develop the disease.

It would be unwise prematurely to assume success or failure in an experiment of this kind; neither should herd testing be applied without full consideration of the protracted nature of the experiment and the practical difficulties involved. The delayed beneficial effect (if any) of this experiment is comparable to that obtained from calf vaccination, with the considerable practical difference that in the latter case infected adults can remain in the herd whilst with blood testing they must be removed as soon as identified. There is a secondary advantage obtained from herd testing that is evident more immediately and appreciated more readily in affected dual-purpose or beef herds. It is better economy to slaughter blood-positive animals when they are in good bodily condition than to continue feeding them for a large proportion to develop into worthless screws. Even if herd testing fails to culminate in eradication, it seems possible that there will be a wish to continue with testing in some types of herd for this reason alone. The great practical difficulties of herd testing arise in dairy herds with a milk contract, and in pedigree herds where animals have a high intrinsic and breeding value. Even in herds of this type, in a number of instances where the blood-test findings have been compared to the development of the clinical disease, it would have been more profitable for the owner to have slaughtered the reactors when detected. For example, in one pedigree herd, of 31 positive reactors found, 29 developed into worthless clinical cases over a period of four years.

An extensive herd test experiment, based on these theories, was commenced late in 1954. It is intended to restrict it to a maximum of 100 herds. Such an ambitious project has not been undertaken solely on the foundation of theory because no unsupported theory would justify an experiment of this magnitude, involving the slaughter of a considerable number of animals. It is usual for theory to be tested out by laboratory experiment before field application. However, not only is the experimental reproduction of Johne's disease a difficult and protracted procedure, but there is considerable reason to question whether the experimental disease produced simulates natural infection. Laboratory experiment was therefore replaced by a pilot experiment in the field, which was commenced in 1951. It was a simple matter to get a number of owners to undertake herd testing, but much more difficult to persuade them to slaughter positive reactors before they showed clinical symptoms. Only three owners at this time were found prepared to fulfil the requirements of this experiment, and two of these later obtained and took advantage of permission to vaccinate and thus became of no further use to the scheme. The pilot experiment, therefore, has resolved into evidence obtained from one herd, where the chronicle of events is of considerable interest. It is a valuable pedigree herd of about 25 milkers and followers, approximately 50 head in all. The husbandry is good but intensive, less than one acre of pasture per animal. The production is high. There was a past history of Johne's disease, and the position had

deteriorated to a number of clinical cases in the year prior to the commencement of herd testing. Between June, 1951, and February, 1956, 12 herd tests have been carried out with the following results:—

June, 1951	5 positive reactors
October, 1951	0 further positives
March, 1952	4 further positives
July, 1952	0 further positives
October, 1952	1 further positive
March, 1953	4 further positives
May, 1953	0 further positives
November, 1953 ...	1 further positive
May, 1954	1 further positive
October, 1954	0 further positives
March, 1955	1 further positive*
February, 1956 ...	0 further positives

Fœtal infection was not appreciated at the commencement of the experiment, and a number of positives were kept in isolation to salvage a calf. The asterisked reactor of March, 1955, was probably infected *in utero;* it is the only animal born since testing commenced that so far has reacted (although about 10 such animals are now in the milking herd), and it was the last survivor of its breeding line.

Smear preparations from the first 10 reactors showed the presence of organisms in all except one animal.

It is of interest that of the 17 blood reactors, eight had shown an avian tuberculin reaction at some time in their test history and nine had not, although of all the animals in the herd between 1951 and the present time 46 have reacted to avian tuberculin one or more times.

The blood test picture suggests successive waves of infected animals reaching a blood-reacting stage.

There has been no clinical disease in this herd since 1952, and if we discount the 1955 reactor as a fœtal infection, no positive blood reaction for two years.

This herd cannot yet be assumed to be clean, but there is definite evidence that the disease has been brought under temporary control. The owner considers the herd has never been in finer over-all condition; it is hoped that his determined adherence to the experiment, which involved the slaughter of some very valuable pedigree animals, will pay him lasting dividends. This is, of course, an uncontrolled experiment, and there is no evidence to show that the disease is not pursuing its natural course and undergoing a regression independent of blood testing and slaughter. The extensive herd trial now in progress should discover whether the findings in one herd have a general application.

The more theoretical and academic aspects of the basal hypothesis must now be considered. It is generally assumed that, apart from intra-uterine infection, the organism is only disseminated by an infected animal through the medium of the dung. There is no evidence to show that any appreciable weight

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of infection is shed by a naturally affected animal until it commences to scour. It must, however, be admitted that this is more a question of the absence of any evidence on this point than of negative findings from attempts to obtain evidence. Organisms can be cultured from the dung as early as one month after experimental infection, but only when very large infective doses are employed; it is noticeable that as the dose used becomes smaller the delay in recovering the organism becomes greater. Where a dose of less than one mgm. of culture has been used (a dose that might well be considered as large) positive cultures have been obtained from the fæces only in very isolated instances during the first post-dosing year. It is questionable, too, whether experimental infection as practised to-day is comparable to the naturally acquired disease. Unless natural infection is a cumulative process it is very doubtful whether anything like the dose required for experimental infection would be ingested. It must be remembered that Johne's disease is found quite frequently in herds with excellent husbandry and exemplary hygiene. Until concrete evidence to the contrary is produced it seems reasonable to doubt, in the case of the natural disease, whether organisms are excreted in the dung before the intestinal wall is in such a state of infection that there is some degree of shedding of the mucosæ. Before this stage of irritation is reached, and scouring occurs, it should be possible to identify the great majority of the infected animals by the blood test. Of the first 955 Johne's-positive bowel specimens received at Weybridge in connection with the work on the complement-fixation test, 90 per cent had been blood-positive animals, and only two per cent definitely blood-negative. In the field it has been the general experience so far that where short-term herd testing (e.g., bi-annual) and eradication of positives has been practised, no further clinical cases occur. The circumstantial evidence of laboratory and field suggests the blood test is effective in identifying animals at some pre-clinical stage of infection. With regard to fœtal infection the present evidence indicates that an advanced stage of the disease must be present in the dam before the placental barrier is broken and such animals should therefore be blood-positive. They should be eradicated before they calve.

No mention has so far been made of non-specific reactions and the margin of error due to false positives. In considering this aspect of the complement-fixation test it should be appreciated that herd application is aimed primarily at eradicating the disease; there are probably no tests of this nature, applied *en masse,* that do not eliminate a percentage of non-infected animals. Before herd testing can be recommended as a routine procedure, however, it is essential that information is obtained as to the false positive percentage involved. In the case of Johne's disease this is an unusually complicated problem. To prove an animal is not infected it is necessary to carry out a complete post-mortem examination and considerable culture work. In cases of doubt there is no animal that can be used for diagnostic purposes comparable to the guinea-pig in tuberculosis. It is still not universally appreciated that scouring and emaciation are only the terminal stages of the disease, and that gross lesions are not invariably present in the bowel even when numerous acid-fast bacilli can be demonstrated in smears

of the mucous membrane. Organisms may be very numerous in some parts of the intestinal tract, and very difficult to demonstrate in other parts. These facts, combined with evidence that infection does not result necessarily in extensive or clinical disease, and that recovery is a possibility, make the identification of negatives difficult. There is really only one proper method of assessing the degree and importance of non-specific reactions, and that is by carrying out an extensive blood-testing experiment on a number of herds with no history of Johne's disease and making complete post-mortem and cultural examination on all reactors immediately. A number of herds are necessary because non-specificity may well be a herd factor; Johne's free herds are indicated because there is already evidence that in some herds in which clinical cases are numerous, these have been accurately forecast by the tests; slaughter should be immediate because of the possibility of recovery. Two instances of recovery from severe clinical disease with numerous organisms being excreted in the scour have been observed. These animals have become blood-negative, completely recovered condition, and are back in their herds. If recovery from extreme disease is possible, recovery from a light infection under suitable conditions would seem to be probable in some instances. The justification for an experiment of this type is a matter of policy, and belief that the complement-fixation test *per se* both warrants and requires the clarification of the non-specificity angle.

The miscellaneous data available on non-specificity show that at Weybridge, of 254 specimens received from non-clinical blood-positive animals, typical organisms were found in 88 per cent by smear technique. These specimens, however, almost all came from herds with a Johne's disease problem. Bovine tuberculosis gives a cross reaction with the Johne's antigen in about 50 per cent of cases, not an important factor in view of the steady progress of attestation in this country, but interesting additional suggestive evidence that the complement-fixation test in mycobacterial infections is an indication of a stage of infection rather than of infection alone. There is no evidence on the effect of avian tuberculosis on the test, possibly because this is usually a very localised and restricted condition in cattle. There is no parallel between the blood test and the avian tuberculin test. Animals with so-called skin tuberculosis sometimes give a blood reaction, but up to the present specimens received from such cases have proved to be affected with Johne's disease as well. It would appear that some of the non-tuberculous udder acid-fast conditions also react, but these are man-made and of unknown extent. It must be mentioned that in some herds with no history, or very rare cases, of Johne's disease a considerable number of blood reactions have been found. In some of these cases the presence of Johne's disease in the herd has been proved, but in others either no specimens have been obtained, or scanty negative material some time after the test was made.

It is almost certain that non-specific reactions do occur, but there is a definite tendency, where blood test findings are not supported by clinical history or gross post-mortem lesions, to ascribe a reaction to non-specificity without satisfactorily demonstrating that the Johne's organism has not been present. If non-specificity is an important factor in blood testing, it is certainly a problem of individual

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herds; observation in some herds has shown that nearly 100 per cent of positive animals ultimately develop Johne's disease.

Summary and Recommendations

1. The principles behind the attempt to eradicate Johne's disease on the basis of the complement-fixation test are discussed, together with the difficulties involved.

2. Herd testing should not be undertaken unless it is the intention to attempt to eradicate the disease by the prompt removal of reacting animals. Miscellaneous herd testing upon the results of which no action is taken, is of no value.

3. The experimental nature of the procedure and its objective of eliminating animals before they can disseminate infection should be made perfectly clear to the owner.

4. The occurrence of additional reactors in successive tests should not be regarded as a breakdown in the experiment. Such an occurrence simply suggests a heavy initial infection with a number of animals in a non-reacting stage of infection when testing commenced. It will only be when calves born after the experiment commenced show evidence of infection that the attempted elimination can be said to have failed.

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THE AERATED BONES OF *GALLUS DOMESTICUS*: THE FIFTH THORACIC VERTEBRA AND STERNAL RIBS

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Introduction

THE following investigation completes a survey, begun and reported on previously by one of us (King, 1956), of the bones which are aerated by the air sacs in adults of *G. domesticus*. In this previous report it was established that, contrary to statements in the literature, the only bones so aerated are the humerus, coracoid, sternum, pelvic girdle, first two vertebral ribs, and vertebræ (except the first two cervical and certain coccygeal). Uncertainty remained, however, about the fifth thoracic vertebra and the sternal ribs: in the relatively small number of birds which was then examined none of these bones was aerated, but Campana (1875), author of the only other comprehensive investigation in this field, said that they were aerated in specimens which he had examined. A further problem encountered at the beginning of this survey, and also commented on by Campana, was the remarkable variation in the degree of aeration in individual birds.

The principal objective of the part of the investigation now to be described was to examine a large number of birds to discover the extent of aeration of the fifth thoracic vertebra and the sternal ribs, and thereby to complete the list of bones aerated in this species. A second objective was to identify any factors which might influence individual variation in the extent of aeration of the skeleton, though it was realised from the outset that this would be difficult because of the nature and sources of the material available.

Material and Methods

The second, third, fourth and fifth thoracic vertebræ were examined in 50 birds, of which two were intact, 13 were carcases previously dissected by students, and 35 had been submitted for pathological investigation at a Veterinary Investigation Centre. We tried to find out if the sex, degree of sexual activity in the female, and the age were related to the variations in the degree of aeration of these vertebræ in the individual birds. The sex was known in 47 birds. Twenty-five of the 37 females could be divided according to the state of their ovaries into those which were sexually inactive and those showing signs of sexual activity. The ages of only four birds were known: these were a four months old pullet, a six months old capon, and two pullets about twelve months old; the others were apparently adults. The breeds were not known.

The sternal ribs were examined in five of these 50 birds; in the others they were damaged or had been removed. All the sternal ribs of another 33 apparently adult birds, of unknown sex and breed, were therefore examined; all these were obtained from the Veterinary Investigation Centre.

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It has been shown that, although injection of the trachea is useful for proving that it is the air sacs which are responsible for aeration, the aerated areas of bones can be accurately distinguished from the non-aerated without injection (King, 1956). Therefore injections were not used in this investigation. The thoracic mass (i.e., the fused second, third, fourth and fifth thoracic vertebræ) was boiled to remove the flesh. The extent of aeration was then accurately established by dissecting the mass with bone forceps. All the sternal ribs of both sides of the body were similarly examined throughout their whole length, except that boiling was unnecessary; the sternal end of each one was examined for pneumatic foramina.

Results

The extent of aeration of the thoracic mass varied greatly (see Table I). The extremes ranged from aeration of only the second thoracic vertebra to complete

TABLE I

Vertebrae fully aerated	Number of birds
T2, T3, T4, T5	7
T2, T3, T4*, T5*	5
T2, T3, T4	17
T2, T3	17
T2	4

* These vertebræ were mainly aerated, but contained some red bone marrow.

To summarise the extent of aeration of the thoracic mass in 50 birds. T = thoracic vertebra.

aeration of the whole mass. The second and third vertebræ were usually aerated, while the fourth was aerated in 58 per cent of the specimens and the fifth only in 24 per cent. The non-aerated areas were generally filled with red bone marrow, but in six specimens they were filled mainly or completely with dense bone.

The first, fourth and fifth sternal ribs were never aerated. In five birds the second or the third rib, or both, were aerated, though very inconsistently (see Table II); the area of aeration was confined to a few millimetres of the sternal extremity, except in one specimen in which the sternal two-thirds were aerated. In all these five birds a small but distinct pneumatic foramen on the cranial or sometimes on the caudal aspect of the sternal extremity opened directly into the aerated area. In four other birds blind-ending fossæ were found in the same place on either the second or third ribs, and sometimes on the first, but these did not lead to any aeration of the bone.

Table III shows the relationship of the sex, degree of sexual activity in the female, and age, to the degree of aeration of the thoracic mass. The degree of aeration appeared to be smaller in the female than in the male, for the males were

TABLE II

Bird	Second rib		Third rib	
	Left	Right	Left	Right
1	++	+		+++
2				+
3				++
4		++++		++
5	+			

To summarise the distribution and degree of aeration of the second and third sternal ribs, in the five birds in which these bones were aerated. The distance which the aerated area extended dorsally from the sternal end of the rib is shown: + = 1 to 3 mm., ++ = 3 to 5 mm., +++ = 5 to 10 mm., ++++ = Most of the rib.

TABLE III

Degree of aeration	Sex		Female sex activity		Age		
	♂ (10 birds)	♀ (37 birds)	Some activity (6 birds)	Inactive (19 birds)	Pullet in lay (2 birds)	6 month capon (1 bird)	4 month pullet (1 bird)
Very aerated	4	8		4			
Moderately aerated	2	12	1	6			
Slightly aerated	4	17	5	9	2	1	1

To relate the degree of aeration of the thoracic mass to the sex, state of female sexual activity, and age. Very aerated = complete or partial aeration of all four vertebræ in the thoracic mass; moderately aerated = aeration of the second, third and fourth thoracic vertebræ; slightly aerated = aeration of the second and third thoracic vertebræ, or of the second alone.

evenly distributed between the extremes of aeration while on the other hand 17 females were slightly aerated and only eight were very aerated. Most of both the sexually inactive and the sexually active females were slightly aerated. The four young birds whose ages were known were all slightly aerated.

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Discussion

These results show that the fifth thoracic vertebra and some of the sternal ribs can be aerated, and so confirm Campana's observation in principle. However, Campana did not mention the relative infrequency with which the fourth and fifth thoracic vertebræ are aerated: our findings indicate that these are aerated respectively in only about 60 per cent and 25 per cent of specimens. Again, Campana implied that any of the five sternal ribs can be aerated, but we found that only the second and third were aerated. Adding the 11 birds reported on in the previous article (King, 1956), the sternal ribs of 49 birds have been investigated, so aeration of the other three ribs must be at least a rarity. In all other respects Campana's account of the aeration of the sternal ribs has been found to be substantially accurate. The incidence of aeration he rightly described as "très-variable et le plus souvent il est nul": the results of the present survey suggest that it occurs in only about 10 per cent of birds. He also described and figured the ventral extremities of the ribs and their pneumatic foramina: "... en même temps elles sont excavées en dessus et en dessous, et, chez quelques sujets, ces excavations ou fossettes sont garnies de pertuis penumatiques: ils existent plutôt dans l'excavation supérieur que dans l'inférieure."

Factors which might influence individual variation in the degree of bone aeration were discussed in the previous article referred to above; the limited material then available indicated that old age alone was not a factor. Our present results are confined to the thoracic mass but it seems reasonable to apply them, with due reserve, to the skeleton as a whole. They provide a little information on the possible significance of age, sex and the degree of female sexual activity. The age was known in four birds, all of which were young. In all of these the extent of aeration was slight. However, the air sacs apparently invade the skeleton after hatching, at about three weeks in the case of the humerus (Selenka. 1866). Therefore it is not surprising that in those of our birds which were only a few months old the thoracic mass was only slightly aerated. Clearly age must be a factor early in post-embryonic growth.

The degree of aeration in the female appeared to be smaller than in the male, and this suggests that sex may be a factor. However, as the ages were not known, this apparent sex difference might be due to an age factor. There was no indication that the state of sexual activity in the female is a factor.

The occurrence of dense bone in the non-aerated areas, as found here in parts of the fourth and fifth thoracic vertebræ, was not seen in the first part of our survey of the aerated bones or mentioned by Campana (1875).

This account of the aeration of the thoracic vertebræ and sternal ribs should complete the survey of aeration in adults of *G. domesticus* made by King (1956). It is now possible to list as follows the bones which can be aerated in this species: the whole of the vertebral column, except the first two cervical and the free coccygeal vertebræ and the pygostyle; the pelvic girdle; the sternum; the first two vertebral ribs; the second and third sternal ribs; the humerus and the coracoid. Except for the small details noted above, this list agrees exactly with

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Campana's (1875). This renders all the more remarkable the persistent controversy and diversity of opinion on this subject, especially in the current English, American and German text-books (reviewed in previous article); it now transpires that Campana solved the problem more than 80 years ago—a sober reminder not to neglect the early literature.

Summary

(1) The extent of aeration of the fifth thoracic vertebra and the sternal ribs of *G. domesticus* has been investigated, in 50 and 38 birds respectively, all but two of which were adults.

(2) The fifth thoracic vertebra was aerated in 12 birds and the second or third sternal rib in five.

(3) This completes the list which King (1956) had put forward of the bones which can be aerated in this species. It also confirms Campana's (1875) findings.

(4) Factors which might influence individual variations in the degree of bone aeration have been considered. Sex, and age (in young birds), may be significant. The state of sexual activity in the female is apparently not significant.

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THE EFFECT OF THE INFUSION OF DEXTRAVEN SOLUTION ON THE BLOOD PRESSURE DURING CIRCULATORY IMBALANCE OF HÆMORRHAGIC ORIGIN IN THE DOG

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Introduction

(1) *Use of infusions.*

THE difficulties concerned with the administration of blood, plasma or plasma substitutes to small animals who need circulatory replenishment due to loss of plasma and/or blood, are often considerable, especially when the fluid supplied is isotonic and therefore necessitates that large amounts be infused slowly. While not losing sight of this fact, there is still the possibility of administering suitable fluid intravenously to the animal that is anæsthetised, either during operative procedure, immediately preceding it or immediately post-operatively. Under these circumstances suitable fluid may easily and expediently be administered as an intravenous drip infusion.

The administration of natural products under these conditions is associated with disadvantages. Whole blood should be matched, and a suitable donor is not easily found and is less easily bled in sufficient quantities. Homologous plasma is unobtainable unless prepared by the practitioner himself, and is unstable and difficult to preserve unless freeze-dried. Heterologous pure serum albumin is difficult to procure.

Experiments were therefore continued beyond those reported previously (Harthoorn, 1953*a*) to make trials of a plasma substitute that might be used effectively in the unconscious animal. In the course of these, a dextran solution was found unsuitable for cases of established shock (1953, unpublished) although its effectiveness as a plasma substitute to prevent shock after blood loss, or for the prevention of impending shock, were not explored. This may seem difficult to accept in the light of the results with Dextraven infusion reported below. It may have been due, however, to the following reasons:

(*a*) The quantity of molecules of the right size (i.e., large enough to remain in the circulation for a sufficient time, and small enough to effect a sufficient oncotic pressure) may have been relatively small in the preparation used, and much larger quantities should perhaps have been infused to obtain a sufficient blood level of effective molecules.

(*b*) Previous trials (V.S.) had shown that when a therapeutically effective amount of colloid solution was diluted with its own volume of physiological (isotonic) saline solution before administration, it would become ineffective, as did half isotonic colloid solution. Reasons were advanced at the time to show why this occurred: the administration of an isotonic solution, of which a large proportion of the molecules were incapable of exerting an effective oncotic

pressure, results in a loss of a proportionate quantity of this fluid from the blood stream. This loss of fluid from the blood stream under conditions of circulatory imbalance caused damage to the blood vessels, so that the state of shock tended to become irreversible and the animal would become refractory to any form of treatment. It was thought that loss of the smaller of the dextran molecules from the blood stream may have acted in a similar manner, so that the larger molecules failed subsequently to exert a noticeable effect, even when the solution was administered in amounts of some 30 c.c./kg. body weight.

(2) *Results of infusion therapy.*

The restoration of the blood volume in cases where blood has been lost through hæmorrhage may seem logical and obvious, while the need to do so in cases of hypotension and shock is less well understood. In spite of this, it may be of advantage to list those deleterious actions in the body caused by blood loss, hypotension and shock, especially under the added influence of anæsthesia, that may be modified or ameliorated through the intravenous infusion of a suitable fluid.

Although hæmorrhage and shock are similar in many of their aspects, we certainly can no longer say with Blum (1878) "shock is hæmorrhage and hæmorrhage is shock." Moon in 1942 studied the problem extensively and listed more than 20 factors, of which approximately half showed a similarity and the other half a dissimilarity between hæmorrhage and shock: placing reduction in cardiac output and peripheral constriction in the first group and coagulation time and hæmatocrit reading in the second.

The whole problem is, however, simplified if we add the condition of hæmorrhagic shock to the comparison, and consider that hæmorrhage may in many cases be only a preliminary to hæmorrhagic shock.

In broad outline, the result of hæmorrhage is either physiological compensation with hæmodilution and a restoration of blood pressure, or else the animal is incapable of accommodating to any extent, but an attempt is made to maintain the venous return through peripheral vasoconstriction and discharge of the blood reservoirs. If, however, these functions are incapable of materially alleviating the condition, the prolonged hypotension following hæmorrhage will in due course give rise to a state of shock (Blalock, 1934). The entity of hæmorrhagic shock, although based on varying criteria, was broadly accepted by later workers and confirmed by experimental result (Zweifach *et al.*, 1944; Frank *et al.*, 1945; Wiggers *et al.*, 1945; Walcott, 1945). It was also our experience that a state of prolonged hypotension, which in its later stages was to all intents and purposes indistinguishable from shock induced by other means, and which resulted in death if left untreated, was readily induced through the agency of repeated small hæmorrhages (Harthoorn, 1954).

This procedure of small hæmorrhages repeated at long intervals is of especial interest. It was found that the nearer the circulatory condition of the animal approached to a state of shock, the more difficult it was to draw off blood in any quantity without precipitating a circulatory crisis. This sensitivity to blood loss appeared to be independent of the residual blood volume, also an amount of

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blood loss that would precipitate a circulatory crisis after, say, two hours of hypotension, could easily have been added to the original hæmorrhage at some time in the early part of the trial, without making any appreciable difference to the state of the animal. The action of the repeated small hæmorrhages in causing shock was thought to operate through adversely affecting the circulatory state of an animal whose compensatory mechanism had already been set at a certain level.

This illustration of the added effect of a repeated factor acting at intervals is interesting from the clinical angle, especially in relation to operations on sick animals or those that have suffered some injury shortly before operation. In this connection a number of adverse factors may act in a similar way to a hæmorrhage in predisposing an animal to hypersusceptibility to blood loss. Even relatively innocuous factors, such as exhaustion due to muscular activity, may affect adversely and predispose to shock (Bergman *et al.*, 1946; Elman and Riedel, 1946), or even diet (Govier, 1943), while the effect of such influences as previous tissue damage may have a very great effect on the survival of an animal after operative procedure, as far as can be judged by the difference this makes to the amount of blood that the animal can lose subsequent to trauma. This was the experience of several workers, who found that the lethal bleeding volume, or the amount of blood an animal could lose, was severely curtailed by previous trauma, such as crush injury or burns (Blalock, 1934; Harkins, 1935), and to this can probably be added a whole host of other factors, such as intestinal obstruction and toxæmia.

To summarise: from the clinical and therapeutic standpoint, severe hæmorrhage and shock cannot be clearly differentiated, because the former without prompt treatment may merge into the latter; blood loss and shock are further connected in so far that the one predisposes to the other. The amount of blood that a healthy animal can lose with impunity bears no relation to the amount that can be lost by an animal that has not completely recovered from, or been restored after, circulatory imbalance: either a previous hæmorrhage or some other factor that might predispose or induce shock, such as trauma and burns.

The effect of the infusion material used in these experiments on the blood pressure and survival of the shocked animal is obvious from the protocols of the experiments. On account of the small scope of these experiments, however, there are several aspects of the ameliorating influence of infusions of therapeutically active material on the animal suffering from circulatory imbalance and shock that are not shown. These have, however, been demonstrated by other workers in a number of studies and may be summarised as follows:—

(*a*) *The action of infusion on respiration.*

In the anæsthetised and hypotensive animal the infusion of isotonic fluid stimulated the respiration in two ways. The first of these is through the alleviation of cerebral anoxia. This was not obvious from these experiments, but was demonstrated by previous experiments, where all respirations were recorded (Harthoorn, 1954); while the hypotension was prolonged, the respiratory rate

tended to fall and, in a few cases, it ceased altogether. This appeared to be initiated by cerebral anoxia, after which the condition would become progressive, i.e., the depression of the respiration still further increased the cerebral anoxia. In all cases the immediate effect of infusion was to stimulate the respiratory rate.

The second way in which infusion will stimulate the respiration in the animal anæsthetised with barbiturates is through the removal of the anæsthetic from the blood stream. The result of the injection of the ordinary doses used for operations is a depression of the respiratory rate, mainly due to a depression of the sensitivity of the respiratory centre (Schmidt and Comroe, 1940 and 1941). In overdosage, the depression is marked or intense. In previous work it has been shown that the infusion of either crystalloid solution or plasma substitutes into the circulatory system will restore the respirations of dogs after they have been depressed through barbiturate overdosage (Harthoorn, 1955). Thus, through the agency of infusion we obtain a stimulation of the respiration through a double action, i.e., the alleviation of cerebral anoxia in cases of hypotension and the dilution of the anæsthetic agent in the blood stream.

It might be opined that all the action of infusion in the first-mentioned case was due to a similar or identical action to that in the second, where dilution of the anæsthetic was thought to predominate. This, however, can be shown not to be so. At the time of the experiments illustrating the phenomenon described in the first group, the hypothesis was offered, and later demonstrated to be fact in the course of the latter group of experiments: that had the apparent alleviation of cerebral anoxia in the first group been due solely or largely to dilution of the barbiturate in the blood, then recovery should have been maintained in every case.

In the case, however, of the infusion of crystalloid solution as attempted therapy for hypotension and shock, it was found that, after a temporary elevation, the blood pressure once more fell to, or below, the pre-infusion states (Harthoorn, 1953*a*). As the blood pressure fell, so the stupor and depression of the respiratory rate once more manifested themselves. In the later experiments, however, where the crystalloid fluid was administered to dilute the anæsthetic agent in the blood stream, it was found that, although the bulk of the infusion must have left the blood stream shortly after administration, the improvement due to anæsthetic dilution was maintained.

The anæsthetic levels used in the course of the first experiments were extremely light. It was suggested at the time that, as many hours elapsed between the commencement of the hypotensive state and the state of hypotension at shock level, followed by two and a half hours at that level before infusion was commenced, the original dose of anæsthetic—or a subsequent dose administered before the commencement of hypotension—must have been very largely detoxicated at the time of infusion. The animal was thus kept unconscious very largely through cerebral anoxia and stupor. This theory was substantiated by the fact that, whereas little or no anæsthetic was needed from the time of commencement of hypotension, and during the space of drastic hypotension, till the time of infusion, regular hourly injections of barbiturate were once more

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necessary after successful infusion therapy had been accomplished. Furthermore, when the blood pressure had once more fallen after its temporary elevation by the infusion of crystalloid solution, and the solution had presumably left the blood stream, the depth of apparent anæsthesia was no lighter than before infusion.

(*b*) *The recovery of extracirculatory (sequestrated) blood.*

The recovery by the circulation of extracirculatory blood through the agency of infusion may also act in two separate ways. It may act through the lowering of anæsthetic concentration; it has been demonstrated (Hausner *et al.*, 1938; Carr and Essex, 1944) that the effect of barbiturate on the spleen is to cause a dilatation with the relative immobilisation of a considerable amount of red blood cells. Other workers (Hemingway, 1941; Green *et al.*, 1943) have found that this sequestration of blood occurs also to some extent in the dilated cutaneous vessels of those animals anæsthetised with barbiturates. Although in the dog this does not make as much difference to the heart output as might be surmised (Wiggers, 1944), it may nevertheless be considered with other factors such as extensive blood loss or circulatory imbalance.

As the degree of the various deleterious influences of barbiturate administration appears to be very closely concerned with the size of the dose (Tatum, 1939), we can assume that from the dilution of the anæsthetic agent in the blood alone, the administration of intravenous fluids should have a beneficial action in respect of the return of extracirculatory erythrocytes.

Secondly, there is the effect of the infusion itself in cases of hypotension where the sequestration appears to be due to compensatory vasoconstriction. Chambers and Zweifach (1944), Zweifach, Lee and others (1944), as well as Shorr, Zweifach and Furchgott (1945), found that in the initial stages of compensation to hypotension there was a hyper-reactivity of the metarterioles and capillary sphincters. This resulted in a by-passing of the capillaries by the blood stream, which was now directed through the main arterio-venous channels or anastomoses. A theory of spastic states of the arterioles in cases of circulatory imbalance was also formulated as a result of their experiments by Fine and others (1945).

Added to this, it was found (Harthoorn, 1953*b*) that in states of shock other than those induced by hæmorrhage, the reduction of circulating plasma volume was much greater than could be confirmed by the increase in the hæmatocrit value. This was explained on the basis that red blood cells disappeared from the circulating blood at the same time as plasma was lost into traumatised tissue. At the same time it appeared that the reduction of the blood (plasma) volume (measured by Evans blue dye T.1824) was disproportionate to what would have been expected from consideration of other factors,* so that it was assumed that the sequestration did not apply to red blood cells alone, but to plasma plus blood cells of very high hæmatocrit value.

* For figures on reduction in circulating plasma volume and increases in the hæmatocrit value, see Harthoorn, 1954.

Calculated another way, this could also be demonstrated. The diagram illustrating the expected and actual hæmatocrit values after infusion (Harthoorn, 1953*b*), showed that the reduction of the hæmatocrit value was far less than calculated. Also, where measured, the oxygen content of venous blood fell steeply immediately after infusion in spite of the improved circulation and increased respiratory rate. This again was ascribed to the mobilisation of red blood cells that had been outside the circulation for some time, as well as to the inclusion into the orbit of the circulation, of tissues that had been outside it and were consequently suffering from a state of stagnant anoxia.

(*c*) *The effect of infusion upon body temperature.*

The effects of barbiturate anæsthesia upon body temperature in this consideration is relatively unimportant, as in any case modern appliances to counteract any drop in temperature due to anæsthesia and operation are in current use. Furthermore, although Hemingway (1941) finds that body temperatures are depressed under barbiturate anæsthesia, our own results were afterwards found to confirm those of Green, Nickerson and associates (1943), that if the level of anæsthesia is light enough, the primary fall is compensated by shivering and cutaneous vasoconstriction to slightly above control levels.

The effect of infusion of plasma, or of fluids that may be considered as plasma substitutes, is very profound on the body temperature that has fallen as a result of the circulatory derangement. Depressions in temperature, of 8° C. or more, were common in reversibly shocked animals lying in a centrally-heated room and further warmed by a large operating lamp (table unheated) (Harthoorn, 1954). In these animals compensatory mechanisms, such as shivering, were in abeyance. Almost immediately upon infusion, shivering, often intense, was exhibited, and the body temperature rose rapidly, often to above control levels.

Although the possibility of heating the animals artificially was not explored, owing to the reports that application of heat to the shocked organism is detrimental and shortens survival rate (Wiggers, 1941; Rosenthal, 1942; Walton, 1944; and Blalock and Mason, 1945), it is to be expected that no maintenance of body heat could be achieved without considerable heating of the outer surface and causing cutaneous vascular dilatation, with consequent adverse effect on the depressed blood circulation.

(*d*) *General consideration in relation to lightening of the (barbiturate) anæsthetic.*

Although many workers (Beecher, 1942; Ingraham and Wiggers, 1945; Ingraham, Roemhild and others, 1947) maintain that barbiturate anæsthesia has no deleterious effect on the animal in predisposing to a state of shock, others report that some effects may be observed. Bouckaert and Heymans (1937) state that barbiturates suppress the carotid sinus reflex, and Wiggers, Ingraham and Dille (1945) found it more difficult to induce hæmorrhagic shock in dogs that were anæsthetised locally instead of being under barbiturate anæsthesia. From these and other reports it appears that barbiturate anæsthesia does not have marked deleterious effects *provided that it is administered slowly and in optimal quantities.* These conditions may not always be obtained in practice, especially

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as the term "optimal quantities" relates to the physiology of the animal and unconsciousness, rather than to any considerations of relaxation for operation.

It seems, therefore, that in cases where there is any question of the advent of circulatory imbalance during operative procedure, it would be advisable to consider therapy from the point of view of the dilution of the barbiturate, and therefore the lightening of the anæsthesia, as well as considerations of the advantages of improving the circulation. From all available reports, natural plasma, with or without the addition of red cells, is still the optimum treatment for shock, but may be substituted by certain other products (see protocols, as well as Harthoorn, 1953*a*). Since it has been shown (Harthoorn, 1955) that resuscitation from anæsthesia by simple dilution may be effected through the infusion of fluids that remain in the blood stream, the therapy for both conditions may be achieved with the same infusion.

Fluids Used for Infusions

The use of dextran solution was mentioned as a blood substitute for dogs by Ogilvie in 1951 among other substances such as gum saline, gelatin, isinglass and polyvinal pyrrolidone.

The last-named, "Periston" (Hecht and Weese, 1943), was used in large quantities as a plasma substitute in Germany during the second world war. It is a synthetic product representing the polymerised form of the unsaturated vinyl alcohol (Heuper, 1942). It appears to be unsuitable for use as a plasma substitute in dogs (Scott, Worth and Robbins, 1944) and probably has a specific deleterious action, similar to that of pectin solution (Hartman, *et al.*, 1937, 1941), as reported by Ivy, Greengard and associates (1943). Isinglass (Taylor and Waters, 1941) is prepared from the swim bladders of fish such as sturgeon and hake. It is essentially similar to gelatin, and the availability of the latter has detracted from its popularity. Isinglass apparently contains a number of impurities (Waters, 1941) and, unlike gelatin, is antigenic (Medicine and War, 1944). Also it was found to be inferior to gelatin by Gordon and others (1942). Gelatin, first used in perfusion experiments by Ringer (1885), was first tested clinically by Hogan (1915). It was tested experimentally on rabbits by Wolfson and Teller (1929) and more extensively during the search for plasma substitutes at the outbreak of the second world war. Reports on the use of gelatin solutions were made by Kozol, Popper and others (1941), who stated it to be effective for the treatment of shock in human patients. Gordon and others (1942) found that gelatin solution occupied an intermediate position between crystalloid solutions and blood in the treatment of blood loss. Similarly, Ivy and associates (1943) found that fewer dogs died as a result of large hæmorrhages when treated with gelatin solution than when treated with physiological saline solution. Little and Wells (1942) found that blood vessels did not appear to be excessively permeable to gelatin solution introduced into the blood stream prior to the infliction of trauma, and the behaviour of gelatin solution in the blood stream of the animal with normal blood pressure was studied by Lawson and Rehm (1943) using both beef-bone and pork-skin gelatin. Their

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findings on the maintenance of gelatin in the normal circulation were confirmed by Little and Dameron (1943). Brünschwig and others in the same year found that injected gelatin was metabolised rather than stored in the body. Gelatin was compared favourably to crystalloid solutions by Ely and Angelo and also by Grodins, both in 1943; and their results were confirmed in the same year by Nichols and others (1943), using gelatin solutions for hæmorrhage, as did Parkins, Koop and others (1943). The lack of toxic effects on injection were confirmed by Robscheit-Robbins and co-workers in 1944. The above-mentioned experiments were concerned with the ability of gelatin to stay in the undamaged circulation, and it was compared to crystalloid solutions in its power to effect resuscitation after hæmorrhage. Trials with gelatin solution on shock (Harthoorn, 1953*a*) indicate that gelatin solutions are not suitable for the treatment of established shock.

Reports on the use of gum saline (acacia) solution, first used by Bowditch in 1871, are too numerous and well-known to be reviewed here. Their unsuitability for intravenous infusion for any condition was reported by Blalock, *et al.* (1932); Beard and Wilson, *et al.* (1932); Maytum and Magath (1933); Good, *et al.* (1934); Christie, *et al.* (1935); Dick, *et al.* (1935) and Studdiford (1937).

The use of dextran as a plasma substitute must be credited to Swedish workers, although Conacher (1951) of Crooks laboratories reports that it was first used by Scheibler in 1874 and investigated by Pasteur 13 years earlier. Extensive trials of dextran as a plasma substitute were reported by Grönwall and Inglemann (1944). It is a polysaccharide of high molecular weight and injection of it damages parenchymatous organs such as the kidney and liver (Grönwall and Inglemann, 1945). Through hydrolysis, however, the molecule can be split to an average molecular weight of about 100,000 and seems to possess most of the virtues of an ideal plasma substitute (Bohmansson and others, 1946; Thorsén, 1949; Bull and others, 1949), as well as the ability to increase the oncotic pressure of the plasma (Wallenius, 1950) and to restore the carotid sinus reflex in dogs after hæmorrhage (van den Heuvel, 1951). Work on the use of dextran for decreasing œdema in nephrotic patients is reviewed by Mollinson and Rennie (1954).

According to Moller, the 6 per cent solution has a similar oncotic pressure to that of plasma, although its viscosity is higher; it is also non-antigenic. He states that, apart from the small amount excreted by the kidneys, the fate of the remainder is obscure, and it is assumed that it is eventually converted into glucose and utilised by the body.

*Dextraven.** The size of the dextran molecule depends on the degree of hydrolysis to which it is subjected; and with a good average size of molecule, there appears to be a tremendous range from minimum to maximum size. The size of the Albumin molecule is approximately 72,000 (Elman and others, 1942), so that the theoretical size of the molecule of a plasma substitute should not be below this, or else the loss into the tissue space tends to be excessive;

* Kindly supplied by Benger's Laboratories, Ltd.

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in fact, as the solution will in most cases be used under conditions of circulatory strain where albumin may already tend to leave the circulation, the optimum size lies rather above the figure of 72,000 (Boyd, Fletcher and Ratcliffe, 1953). Wallenius (1950) thought that the smaller molecules which left the blood stream would set up a counter oncotic pressure to draw fluid from the blood stream into the interstitial fluid. When the molecule becomes much larger, the oncotic pressure for a given concentration will necessarily be less and therefore it will be incapable of maintaining an adequate balance between the intracirculatory and the intercellular fluids, as well as tending to cause organic damage.

According to the makers, it has been possible to fractionate dextran so that there is a great increase in molecules of 130,000 to 250,000, which were found the most efficient in maintaining the circulation, so that those above 250,000 are eliminated and those below that size reduced to 30-40 per cent, a high proportion of the remaining molecules closely approaching the requisite minimal size of 130,000. It was the fractionated product, marketed under the name of Dextraven, that was used in the experiments reported here.

Procedure

(1) *Comparison of methods with those used in previous experiments.*

The range of these trials to test the efficacy of Dextraven solution in resuscitation from circulatory imbalance and shock was small, and the only criteria used were the blood pressure and the survival of the subject. Experience gained, however, in more extensive experiments, where detailed procedure was carried out, such as measurement of the circulating blood volume, blood gas analysis, etc. (Harthoorn, 1953*b* and 1954), showed that it was possible to gauge the degree of shock with simple apparatus and a small amount of experimental procedure. These earlier experiments showed that if, as the result of some shock-inducing mechanism such as loss of blood or trauma, the blood pressure would remain (without artificial depression) at shock level, i.e., about 70 mm.Hg., for a space of some 2½ hours, the animal's condition would be growing progressively worse and its chance of survival without assistance would be negligible. They showed that during this period of hypotension following on, say, blood loss, the animal would at one point commence to show definite signs of *progressive* circulatory imbalance, as evinced by a continuous decrease in the circulating blood volume and a continuous increase in the hæmoconcentration.

During this period mentioned above, when the subject showed a progressively diminishing circulating blood volume, the blood pressure would show no marked fall. The blood pressure would, in fact, be maintained at reasonable levels until circulatory decompensation and just before death. On the other hand, neither would it show any real tendency to rise. In all control animals previously observed, the lack of a rise in the blood pressure during this minimum period of 2½ hours was synonymous with a lack of compensation and the subject did not survive unless its circulation was restored with a fluid that was capable of remaining in the circulation and of exerting a definite oncotic pressure after it had been introduced.

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It has therefore been assumed for the purposes of the trials reported in this paper that:

(*a*) If, subsequent to a number of repeated spaced hæmorrhages, the blood pressure fell to shock level and remained there, showing no tendency to rise for a minimum period of 2½ hours, the animal in question would not survive unless given a suitable treatment.

(*b*) If, as a result of infusion subsequent to the period of hypotension, an animal survived, then the fluid used in the infusion was one that was capable of remaining in the circulation and of exerting a suitable oncotic pressure after it had been introduced.

In these experiments the fluid was tested only against shock that was the result of hæmorrhage. Consequently no claim can be made as to its efficacy against shock other than of hæmorrhagic origin. On the other hand, during earlier experiments it was found that all substances that were suitable for the treatment of hæmorrhagic shock were also suitable for any form of shock tested which was associated with a progressive lowering of the circulating blood volume.

(2) *Methods used.*

The experiments on the resuscitation of animals from hæmorrhagic shock were performed on the following lines:

Anæsthetic. During the administration of the anæsthetic* care was taken to prevent the administration of even a slight overdose: the dose was calculated from the animal's body weight and three-quarters of this dose was slowly administered into the radial vein. The animal was then allowed 15 to 20 minutes to equilibrate, after which anæsthetic was administered in the same way until the desired level of anæsthesia was obtained. At this level, relaxation was fair; the eye reflexes were partially abolishd, so that there was usually no corneal reflex, but a reflex movement might still be obtained from touching the eyelid or inner canthus; the pedal reflex was depressed, and tendon reflexes exaggerated. When anæsthetic is administered in this way, the respiratory rate is only slightly depressed, but respiration is deepened. The body temperature, after a short initial fall, resumes normal level. The blood pressure tends to be slightly raised.

Hæmorrhage. After the animal had been anæsthetised and the blood pressure had been recorded, it was allowed to bleed through a side arm of the cannula in the femoral vein, which was the same as that used to record the blood pressure. This was done to minimise operative procedure. Before the first hæmorrhage, heparin was administered to prevent clotting. This was necessary because the cannula was inserted rather distally in the femoral vein and was therefore of only small size, and also because the clotting time of the blood would be reduced in the early stages of the experiment, while the animal was suffering from hæmorrhage only.

The method of "stepwise" bleeding was employed, where a small proportion of the animal's blood volume, as estimated from the body weight, is removed at a time, with considerable intervals between the bleedings. It had

* Pentobarbitone sodium (Nembutal), Abbots Laboratories, Ltd.

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been found previously that with the use of this method, the subject would go into a state of maintained hypotension after removal of a small proportion of the blood volume. With this method the amount of blood that had to be removed to attain a state of maintained hypotension was less than if a rapid hæmorrhage was employed, and therefore the animal suffered less from profound oligæmia, and was not suffering from actual exæmic shock. A further advantage is that with this method the condition of the animal could be more carefully controlled. With a massive and rapid hæmorrhage the subject usually either compensates, and the blood pressure rises, or else becomes rapidly worse, and the blood pressure falls to an undesirably low level. With the method used, the height of the ultimate blood pressure could be carefully controlled, and usually showed no tendency to rise after it had been brought slowly to shock level. In this way the hæmorrhage resembled more closely the type of hæmorrhage obtained after an operation or that for which the operation is being performed.

Infusion. The solution for infusion was warmed immediately before, but not during, infusion. The warming was effected more to obtain a standard temperature in previously opened, and therefore refrigerated, bottles than in belief in the value of providing a warmed solution.

The rate of flow was adjusted in such a way that approximately 5 c.c. per kilogram body weight was administered in half an hour. The amount of solution infused, 20 c.c. per kilogram body weight, was arbitrary. In experiment 3, where the rate as well as the amount was exceeded, the infusion of a larger amount over the period of two hours appeared to confer no extra benefit, while experiment 1 seems to indicate that much less than the 20 c.c. per kilogram body weight used would have been adequate in that case.

The infusion was given into the radial vein, using a small bore intravenous-type needle, held in position with adhesive tape.

Cannulation. The insertion of the cannula into the femoral artery was effected with the minimum of trauma. To ensure this the artery was exposed in a more distal region than is usual. After exposure, a sterile glass cannula was inserted under asceptic precautions. The exposed area was then thickly coated with pencilllin ointment, both to prevent dehydration of the tissues as well as to prevent contamination. The skin was kept approximated with a towel clip. In no case did this incision subsequently fail to heal rapidly and without complications.

Recording of the blood pressure. As only the mean blood pressure was required, the recording was made with a mercury manometer, using heparinised saline solution as the transmitter fluid. The blood pressure was recorded every half-hour. (*a*) to ensure that there was no rise in the blood pressure during the period of hypotension, and (*b*) to keep a record of the improvement in condition after the infusion had commenced, and in some cases after it had ceased. The period of hypotension was measured as from the last time that the animal was allowed to bleed, i.e., in no case was blood removed during the period of recorded hypotension to maintain the blood pressure at shock level so that the

hypotension was recorded as a symptom and was not regarded as an artifact to induce shock.

Post-infusion treatment When the experiment was regarded as terminated, the femoral artery was ligated with sterile suture material. More penicillin ointment was applied and the skin sutured with nylon. The animal was removed from the table and wrapped in a blanket. The subject had access to water as soon as it had recovered sufficiently from the anæsthetic to drink. In all cases the animals appeared in good spirits on the following morning, showing no symptoms apart from anæmia. No further treatment was therefore required, apart from the normal kennel routine. They were subsequently observed as regards normal deportment and appetite for a period of at least ten days.

Results and Discussion of Protocols

This series of experiments suffered from the following defects: There were no control animals to demonstrate the lethal quality of the shock induced if left untreated; there were no experiments using a crystalloid solution to demonstrate that a fluid of oncotic pressure was essential for the therapy of shock of the severity induced here; there were no experiments using plasma which, as the classical treatment for shock, may have given an indication of the comparative efficacy of the Dextraven treatment. The effect of the infusion of Dextraven solution as described here will therefore be compared to plasma infusions and infusions of crystalloid solutions as performed for the same type of shock in previous trials.

The general effect of the infusion of Dextraven solution at the rate used here (i.e., about 10 c.c. per Kg. body weight per hour) was a rise in the blood pressure and an amelioration of the condition of the animal. The rise in the blood pressure compared very favourably with the rise obtained in previous experiments, using plasma as the therapeutic agent; in fact, the curve when plotted shows no essential differences between the two. In neither plasma therapy nor Dextraven therapy did the blood pressure return competely to normal during the time that the blood pressure was measured, but in both cases this was in all likelihood due to the method of infusion rather than to the product (Harthoorn, 1953*a*) and seems to be a disadvantage pertaining to all isotonic infusion fluids. It did not appear in this case to influence the survival rate. It is suggested that the rate of infusion as used here, i.e., 20 c.c. per Kg. body weight in two hours, is intermediary between the more rapid rate of infusion of the same amount in about half an hour and the method of intermittent infusion, where small quantities are administered with definite time intervals. The latter method has been shown to result in considerably smaller mortality and a better restoration of the blood pressure than the former method.

The administration of the full infusion over a period of some two hours, although using a longer period than in previous experiments, was in all probability still rapid. The animals, which in previous experiments died after therapy by substances such as plasma, exhibited on autopsy hæmorrhagic effusion of the intestinal wall, with free blood in the lumen of the intestine.

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The passing, in case 1, of hæmorrhagic fæces coated with a gelatinous substance that resembled Dextraven, seemed to indicate that death from visceral effusion might have occurred in that case also. It seems from these results (experiment 1 and previous experiments) that the blood vessels of the viscera are particularly susceptible to strain through increase of the circulation with too great a rapidity, probably due to the damming back of the portal circulation. This would suggest that in practice the infusion might be given at a slower speed in cases where the degree of circulatory imbalance appears to be grave; this might be further improved by giving the infusion at two different speeds, the first 5 c.c. per kilogram being administered at a fairly rapid rate to give the circulating fluid a certain amount of volume, and the rest of the infusion at a slower speed than employed here.

The result of infusion in the second case (2) at first sight appears to be only partially effective. On the other hand the blood pressure during the last hour, and one hour after the termination of infusion, was still improving. Three hours after the commencement of infusion is not a very long time in which to measure recovery, and if the animal had been observed over a longer period the blood pressure may have risen to one closely approaching normal. To obtain a real impression of the recovery of any animal subsequent to hypotension, the blood pressure should be recorded until it reaches a prolonged plateau level. The excellent condition of the subject on the following morning seems to indicate that the blood pressure must have reached a normal figure before morning.

The same criteria apply also to the other experiments, especially to number 3. In experiment number 5, where the blood pressure was measured for an hour longer than in the others, it can be seen that the blood pressure continued to rise until the end of the time of observation. Number 4, where the blood pressure could be recorded for only two hours, showed during this time a blood pressure rise commensurate with recovery similar to the others.

The results may be summarised by saying that an infusion of Dextraven solution into dogs suffering from hæmorrhagic hypotension and shock was effective in inducing a rapid and sustained rise in the blood pressure in every case. Ultimate survival on a good plane of health for at least 10 days was found to result in all cases (4) where survival of the animal was permitted.

Summary

(1) A state of hæmorrhagic hypotension was induced in five dogs under light pentobarbitone sodium anæsthesia.

(2) The animals were considered to be in a state of shock on the sole criterion that the blood pressure failed to show a rise during a period of $2\frac{1}{2}$ hours after the commencement of a level of hypotension at shock level and after the last hæmorrhage.

(3) In all cases the infusion of Dextraven solution resulted in a sustained rise in the blood pressure and in the four cases observed, in complete survival and in restoration to good health.

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PROTOCOLS

(Body weight expressed to nearest half kilogram.)

(1) Mongrel (female). Body weight 10 kg.
Anæsthetised and blood pressure registered in femoral artery.
Pressure mean 150 mm. Hg.
Hæmorrhage to blood pressure of 60 mm.
After 2½ hours „ „ „ 50 mm.
Infusion commenced.
At commencement blood pressure 50 mm.
After ½ hour and infusion of 50 c.c. blood pressure 90 mm.
„ 1 hour „ „ „ 100 c.c. „ „ 115 mm.
„ 1½ hours „ „ „ 150 c.c. „ „ 135 mm.
„ 2 hours „ „ „ 200 c.c. „ „ 140 mm.
Infusion stopped.
After another hour blood pressure 140 mm.
Hæmorrhagic fæces were passed during second half hour after infusion.
Survived (appetite good following morning).

(2) Mongrel (female). Body weight 12½ kg.
Anæsthetised and blood pressure registered in femoral artery.
Pressure 165-170 mm. Hg.
Hæmorrhage to blood pressure of 70 mm.
After 2½ hours „ „ „ 65-70 mm.
Infusion commenced.
At commencement blood pressure 65-70 mm.
After ½ hour and infusion of 80 c.c. blood pressure 95 mm.
„ 1 hour „ „ „ 150 c.c. „ „ 115 mm.
„ 1½ hours „ „ „ 280 c.c. „ „ 120 mm.
„ 2 hours „ „ „ 350 c.c. „ „ 130 mm.
Infusion stopped.
After 3 hours blood pressure 135 mm.
Survived (appetite excellent following morning).

(3) Mongrel (male). Body weight 17½ kg.
Anæsthetised and blood pressure registered in femoral artery.
Pressure 135 mm. Hg.
Hæmorrhage to blood pressure of 50 mm.
After 2½ hours „ „ „ 55 mm.
Remained at 55 during remaining 2 hours.
Infusion commenced.
At commencement blood pressure 55 mm.
After ½ hour and infusion of 150 c.c. blood pressure 85 mm.
„ 1 hour „ „ „ 300 c.c. „ „ 100 mm.
„ 1½ hours „ „ „ 450 c.c. „ „ 110 mm.
„ 2 hours „ „ „ 540 c.c. „ „ 120 mm.
Infusion stopped.
After 3 hours blood pressure 125 mm. Hg.
Survived. (Next morning slight dullness but appetite normal. By evening completely normal.)

(4) Mongrel (female). Body weight 12½ kg.
Anæsthetised and blood pressure registered in femoral artery.
Pressure 145-150 mm. Hg.
Hæmorrhage to blood pressure of 55 mm.
After 2½ hours „ „ „ 50-55 mm.
Infusion commenced.
At commencement blood pressure 50-55 mm.
After ½ hour and infusion of 60 c.c. blood pressure 85 mm.
„ 1 hour „ „ „ 120 c.c. „ „ 107 mm.
„ 1½ hours „ „ „ 185 c.c. „ „ 120 mm.
„ 2 hours „ „ „ 250 c.c. „ „ 128 mm.
Infusion stopped.
During the next hour the arterial cannula became detached while in charge of an assistant, and the animal was destroyed by an intracardial injection of chloroform as pre-arranged.

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(5) Mongrel (male). Body weight 10½ kg.
Anæsthetised and blood pressure registered in femoral artery.
Pressure 145 mm. Hg.
Hæmorrhage to blood pressure of 55 mm.
After 2½ hours „ „ „ 47 mm.
Infusion commenced.
At commencement blood pressure 47 mm.
After ½ hour and infusion of 50 c.c. blood pressure 75 mm.
„ 1 hour „ „ „ 70 c.c. „ „ 97 mm.
„ 1½ hours „ „ „ 130 c.c. „ „ 115 mm.
„ 2 hours „ „ „ 170 c.c. „ „ 128 mm.
Infusion stopped.
After 3 hours blood pressure 136 mm.
„ 4 hours „ „ 140-142 mm.
Survived (next morning playful and with good appetite).

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A CASE OF *CEPHALOTHORACOPAGUS MONOSYMMETROS* IN THE BOVINE SPECIES, FROM THE CLINICAL AND ANATOMICAL ASPECTS*

By J. W. DRANSFIELD, M.V.Sc., M.R.C.V.S., and
P. J. N. PINSENT, B.V.Sc., M.R.C.V.S.
University of Liverpool

PART I—SURGICAL ASPECTS OF THE RELIEF OF DYSTOKIA, IN THIS CASE BY CÆSAREAN SECTION.

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THE subject of this report was a two-year-old Friesian heifer in labour with her first calf. No progress had been made three hours after second-stage labour commenced, and the owner's veterinary surgeon was called in. He examined the animal, decided immediately that she could not be calved by normal methods, and sent her forthwith to this Field Station.

The heifer arrived in good condition, active and bright. She was not straining and did not appear distressed. Vaginal examination revealed that the cervix was fully open and that two forelegs and a head were present in the vagina. The digits were just within the vulva and the right leg appeared to be deformed in that the knee was twisted outwards. A third limb was also present in the vagina, curving over the back of the neck with the digit lying on the right-hand side of the fœtal head. It was impossible to pass the hand into the uterus itself as no room was available between the calf and the pelvic bones, nor could the calf be moved in either direction. It was considered that the fœtus was probably a *Schistosomus reflexus* and Cæsarean section was carried out in the manner usually adopted at this Institute (Wright, 1953) using a left paramedian incision with the animal in dorsal recumbency under general anæsthesia.

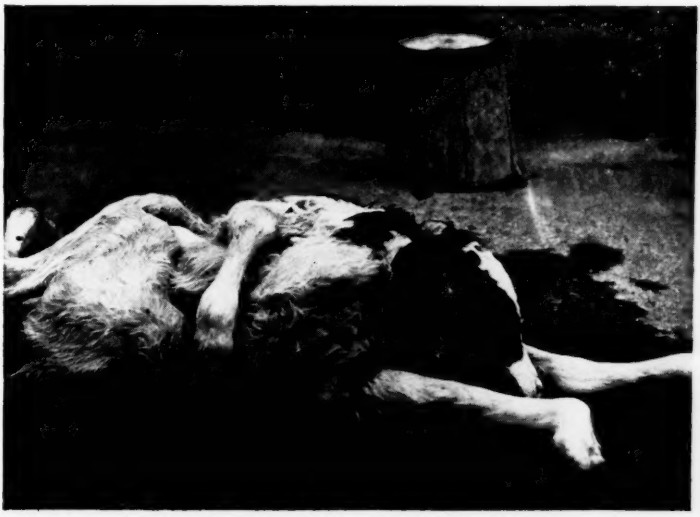
Anæsthesia was induced by the slow intravenous injection of 50 grams of chloral hydrate in 500 c.c. water, and was maintained very satisfactorily throughout the operation by the additional slow intravenous injection of a total of 25 grains of nembutal.

The incision was carried down to peritoneum and the abdomen entered. The two layers of omentum which lie beneath the incision at this site were opened and the uterus exposed. It was found impossible to bring this organ up into the incision, so it was opened in the abdomen, making an eight-inch incision. The allanto-chorionic membrane and the amnion were cut, and a manual examination of the fœtus was attempted. Several fœtal limbs could be palpated,

* This paper is devoted to the consideration of a fœtal monstrosity removed from a parturient Friesian heifer by Cæsarean section, and describes both the surgical aspects of the case (P.J.N.P.) and the anatomical details of the fœtus (J.W.D.).

A case of *Cephalothoracopagus monosymmetros* in the bovine species.

A. Viewed from above.



B. Viewed from the right.

(*Article by Dransfield and Pinsent, page* 300)

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but their arrangement was most confusing and it was impossible under the circumstances, hampered by the fœtal membranes and uterine wall, to make a sufficiently detailed examination to determine the exact nature of the abnormality. It was, at all events, not a *Schistosomus* and, further, it was alive as fairly vigorous limb movements were occurring. At this point it appeared possible that the case might even be one of twins.

Eventually two hocks were identified as belonging to the same fœtus and they were pulled up to the incision and the feet manœuvred through. Snares were applied and a normal hindquarters and tail were drawn out of the incision to a point just behind the fœtal thorax. No further progress could be made, and it was impossible to pass a hand between the lip of the incision and the fœtus to determine the cause of obstruction, and equally impossible to push the hindquarters back into the uterus, it was decided to remove the whole of this part. This was done with a butcher's knife, section being made as far forward as possible, and the stump pushed back. It was now the intention to bring the head and forelegs up through the incision. The forelegs were readily found and drawn through the incision but the neck appeared to be stiff, and the nose could not be brought into line with the forelegs. The head and neck were amputated with embryotome wire as near to the thorax as possible, lifted out of the uterus, and temporarily discarded without examination. This was unfortunate, as detailed examination of the head would have given the operator a more accurate indication of the nature of the monstrosity.

Progress was becoming difficult as the operation field was almost completely obscured by fœtal membranes, uterine fluid, fœtal blood, gut, and body organs, and it was now quite impossible to keep the uterine incision up to the abdominal incision. It will be appreciated that considerable quantities of these substances were passing into the maternal abdomen.

It was now hoped that traction on the protruding forelegs would deliver the fœtus but, in fact, the result was to impact the fœtus in the incision, and no further progress could be made. The uterine wall was already severely torn in several directions, and the operator was unwilling to extend this tear further, either by forced traction or with a knife, as he envisaged the possibility of the uterus being beyond surgical repair.

With considerable misgiving, as it was believed that no adequate point for traction would remain available, both forelegs were removed at the shoulder by subcutaneous dissection, and the thorax pushed back into the uterus. Sufficient room had now been gained within the uterus to make a proper manual examination of the remainder of the fœtus. The thorax was grossly misshapen and very much wider than that of a normal calf; it possessed another complete pair of hindquarters and another pair of forelegs and it was now obvious that, quite apart from the size of the thorax, these appendages had contributed considerably to the failure of attempts to deliver the fœtus by traction upon the other extremities.

The remaining hindquarters were set on at an angle to the longitudinal axis of the thorax, and thus obstructed attempts to rotate the thorax in order

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to bring the remaining forelegs out of the incision. The hindquarters were therefore drawn out of the incision and cut off as close to the thorax as possible with a knife. It was now possible to bring the forelegs out of the incision and in order to reduce the enormous width of the abnormal thorax, one of them was removed at the shoulder leaving the other for traction. Even now it was obvious that neither the already formidable uterine opening, nor the incision in the abdominal wall, were large enough to deliver the fœtus without uncontrolled tearing of the uterus, and further severe damage to the badly bruised and lacerated musculature of the abdominal wall. The original ten-inch abdominal incision was therefore extended forwards for a further four inches, and the uterine tear carried forwards for a similar distance. Fairly vigorous, but controlled, traction now effected removal of the fœtal thorax.

Anæsthesia remained perfect, and respirations were regular and quiet. The uterine tear was located within the abdomen and brought up to the abdominal incision, and as much of the fœtal blood, fæces, and tissues as possible removed from the maternal abdomen. The fœtal membranes were firmly adherent and were left *in situ*, and the large star-shaped aperture in the uterus closed with a number of continuous Lembert sutures, one to each point of the star, the central portion of the star being closed with a separate continuous Lembert suture.

The abdominal incision was closed in the usual manner, although a large number of supplementary sutures were inserted to close the numerous ragged tears in peritoneum and muscular layers. Three megaunits of penicillin were introduced into the abdomen before final closure, and the muscle edges were dressed with intramammary penicillin. From first to last the operation took two hours and forty minutes. The heifer was given two megaunits of penicillin, ten c.c. of Phenergan (May & Baker) and ten c.c. of pituitrin, intramuscularly, and was then well rugged up, propped in sternal recumbency, and left for the night.

To our surprise the animal made an uneventful recovery. She passed the fœtal membranes during the night, was up and eating a little the next morning, and her condition showed a steady improvement until on the sixth day after operation her behaviour and appetite were normal. She was given three megaunits of penicillin, intramuscularly, daily, for the first three days.

Body temperature was 102.5° F. on the first post-operative day, and by the fifth day it remained level at 102° F. Pulse, however, was 180 and very irregular on the first day, and even when the patient was discharged twenty-eight days later it was still between eighty and ninety and somewhat irregular. It is possible that this animal always had an abnormal pulse-rate. A fair amount of creamy white vaginal discharge occurred during the second post-operative week, but this had ceased before the heifer was discharged.

Some sepsis of the abdominal wound occurred, and at the end of the second week the skin wound was reopened to allow evacuation of pus, and necrotic muscle tissue which contained unabsorbed gut sutures. The muscle layers, however, did not break down, and the wound had almost healed completely by granulation when the heifer was discharged.

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On the day following operation the portions of the fœtus were reassembled, and both the limbs and the body organs were sutured, as far as was possible, into their original position. The reassembled fœtus weighed 67 lb. A preliminary examination gave the impression that the monster was the result of incomplete separation of twins. It possessed one head and neck, the head possessing two pairs of ears. The neck widened out into two thoraces, fused sternum to sternum, each thorax possessing a completely formed hindquarter and tail, and each possessing its own pair of forelegs which were clasped around the common neck. This fœtus appeared to merit detailed examination and was sent to the Department of Veterinary Anatomy, its description forming the subject matter of the second part of this report.

Although the primary object in presenting this paper is to report the anatomical features of the fœtus, it is felt that the description of the technical difficulties encountered in its removal by Cæsarean section may serve a useful purpose. In the first place, it is almost incredible that the peritoneal cavity of any animal is able to withstand the severe and prolonged interference and gross contamination which occurred in this case. Had there been any delay and, in particular, any prolonged vaginal interference, before operation commenced, the heifer must have died, as the contents of the uterus would have been grossly infected and a very severe peritonitis must have occurred. In this case probably the uterine contents were virtually sterile.

It seems obvious that the credit for the successful outcome of this operation must be due, firstly, to the owner, who sought professional advice immediately he suspected the possibility of abnormality, and, secondly, to the veterinary surgeon, whose action resulted in the animal arriving here only four and a half hours after second-stage labour commenced, rather than to the efforts of the surgeon and his assistants.

In the second place, the writer believes that the successful outcome of the operation itself was linked very largely with the adoption of the recumbent position and the attainment of completely satisfactory anæsthesia and relaxation.

Finally, a brief consideration of the economical aspects of this case may not be out of place. The majority of cows provide a reasonably normal milk yield following Cæsarean section and a proportion conceive again. At the owner's request this animal was not milked, was dry when sent home, and although subsequently served three times she did not conceive. This is not surprising in view of the great damage incurred by the uterus and the probable extent of the adhesions which must have involved that organ. She was fattened at grass for five and a half months, and dead weight at slaughter as a cow-heifer was 680 lb. The financial return must be considered as very satisfactory when set against the sole alternative, which was the knacker value at the time of parturition. It is possible that this return might have been even more satisfactory had the owner availed himself of the animal's milk yield before fattening her.

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NEWS

Export of Horses to Europe

THE Minister of Agriculture, Fisheries and Food, and the Secretary of State for Scotland have made an Order increasing the values below which certain categories of horses cannot be exported to European countries. The old and new minimum values are:—

	Old	*New*
Heavy draft horse ...	£80 ...	£105
Vanner, mule or jennet ...	£75 ...	£100
Ass	£10 ...	£20

The new rates are designed to take account of changes in money values and price movements since the minimum values were last increased in 1950. The Order, entitled the Exportation of Horses (Minimum Values) Order, 1956, comes into operation on June 4, 1956, and may be obtained from H.M. Stationery Office (price, 2d. net).

Note

Under the Diseases of Animals Act and Orders, horses being exported to European countries (subject to a number of exemptions, mainly for high-quality animals), are required to be examined at the port of embarkation by a veterinary inspector who must certify before they are allowed to embark that they are fit to travel and to work without suffering. In the case of heavy draft horses, vanners, mules, jennets and asses the veterinary inspector must also be satisfied that they are not more than eight years old and of not less than the specified values.

NOTICE

BURROUGHS WELLCOME & Co. announce the introduction of "Wellcome" brand Ovine Enzootic Abortion Vaccine (Kebbing Vaccine). This egg-adapted adjuvant vaccine, prepared at The Wellcome Research Laboratories, is intended for the prevention of enzootic abortion in gimmers and ewes and is injected subcutaneously in a dose of 1 c.c., before tupping.

"Wellcome" brand Ovine Enzootic Abortion Vaccine (Kebbing Vaccine) is issued in containers of 20 c.c.

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